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Cancer patients with venous thromboembolism: Diagnostic and prognostic value of elevated D-dimers

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Abstract

Background: D-dimer testing is known to have a high sensitivity at simultaneously low specificity, resulting in nonspecific elevations in a variety of conditions.

Methods: This retrospective study sought to assess diagnostic and prognostic features of D-dimers in cancer patients referred to the emergency department for suspected pulmonary embolism (PE) and deep vein thrombosis (DVT). In total, 526 patients with a final adjudicated diagnosis of PE ($n = 83$) and DVT ($n = 69$) were enrolled, whereas 374 patients served as the comparative group, in which venous thromboembolism (VTE) has been excluded.

Results: For the identification of VTE, D-dimers yielded the highest positive predictive value of 96% (95% confidence interval (CI), 85–99) at concentrations of 9.9 mg/L and a negative predictive value of 100% at .6 mg/L (95% CI, 97–100). At the established rule-out cut-off level of .5 mg/L, D-dimers were found to be very sensitive (100%) at a moderate specificity of nearly 65%. Using an optimised cut-off value of 4.9 mg/L increased the specificity to 95% for the detection of life-threatening VTE at the cost of moderate sensitivities (64%). During a median follow-up of 30 months, D-dimers positively correlated with the reoccurrence of VTE ($p = .0299$) and mortality in both cancer patients with VTE ($p < .0001$) and without VTE ($p = .0008$).

Conclusions: Although D-dimer testing in cancer patients is discouraged by current guidelines, very high concentrations above the 10-fold upper reference limit contain diagnostic and prognostic information and might be helpful in risk assessment, while low concentrations remain useful for ruling out VTE.

Leon D. Gruenewald and Evangelos Giannitsis contributed equally to this work to share the last authorship.

KEYWORDS
cancer, D-dimer, deep vein thrombosis, pulmonary embolism, venous thromboembolism

1 | INTRODUCTION

More than 150 years ago, Armand Trousseau was the first to describe the relationship between malignancies and cancer-associated venous thrombosis in patients presenting with *phlegmasia alba dolens* caused by deep vein thrombosis (DVT) of the leg and migratory thrombophlebitis.[1] A large body of subsequent studies has consistently confirmed Trousseau's preliminary findings linking the occurrence of cancer-associated venous thromboembolism (VTE) to a poor prognosis and underlining the requirement for a different approach to prevention and treatment.[2] A study including more than 34,000 cancer patients reported a 2.2-fold higher mortality rate in patients with confirmed cancer at the time of primary VTE compared to matched controls without VTE.[3] These findings suggested the presence of advanced and more aggressive disease and could not be explained by the extent or type of cancer disease. The risk of developing VTE that includes DVT and pulmonary embolism (PE) is approximately four- to sevenfold elevated in patients with cancer.[4] Data from 4466 enrolled cancer patients receiving chemotherapies have shown that about 10% of patients die from thromboembolic events,[5] making VTEs one of the leading non-cancer causes of death.

Given recent advances in diagnostic imaging modalities and treatment strategies, the improved survival of cancer patients has led to a further increase in the incidence of cancer-associated VTE. D-dimers represent fibrin degradation products that can be quantified to rule out VTE in specific patient populations and conditions.[6] However, D-dimers are not recommended for ruling in VTE given their lack of specificity.[7] Elevated D-dimer values can be seen in various conditions, such as aortic dissection, pregnancy, infection, trauma or malignancy limiting their usefulness due to inappropriate specificities.[8,9] Despite its well-known clinical relevance, the diagnosis and risk stratification of suspected cancer-associated VTE remain challenging. Identification of high-risk groups would allow for close monitoring and the initiation of appropriate treatment.

Thus, we aimed to establish specified D-dimer cut-offs for the identification and risk stratification of cancer patients with VTE in a large cohort of subjects having increased D-dimers for various reasons. A secondary study goal was to focus on management strategies in the case of highly elevated D-dimer values.

2 | METHODS

This retrospective study was approved by the institutional ethical review board and complied with the Declaration of Helsinki. Written informed consent was waived.

2.1 | Study population and design

We identified a total of 5573 patients who were referred to the emergency department of the University Hospital Heidelberg (Germany) for suspected VTE with a broad range of symptoms including dyspnoea and atypical chest pain. Among these, 526 patients had an underlying cancer diagnosis with available D-dimer testing. In all cases, the diagnosis of cancer preceded the event of thromboembolism and the referral to the emergency department. While cancer patients with confirmed VTE represented the positive cases, those with D-dimer elevation for various other reasons formed the controls after exclusion of VTE using compression ultrasound (CUS) or computed tomography angiography (CTA). Aside from cancer, the comparative group of cancer patients without VTE included vascular (e.g. peripheral arterial disease, aortic dissection), gastrointestinal (e.g. gastritis, ulcer), cardiac (e.g. acute myocardial infarction, hypertensive crisis), extracardiac (e.g. pneumonia, chronic obstructive pulmonary disease, bronchial asthma) and orthopaedic (e.g. joint pain, arthritis, trauma) conditions.

The determination of D-dimers was performed at the attending physician's discretion in the emergency department immediately after admission. Based on the institutional protocol and latest guidelines,[10,11] patients with elevated D-dimer values and clinically suspected VTE were subjected to either CUS or CTA, excluding high-risk groups of patients with hemodynamic compromise who received immediate rescue reperfusion therapy. For the exclusion of DVT, CTA was performed only in cases without clear evidence of DVT in CUS and persistent suspicion (four cases of in total 69 patients). Collected data at admission included patient characteristics, history, physical examination, diagnostics and treatment. The evaluation of clinical probability for the presence of VTE was based on the original version of the Wells score.[12] Upon suspicion of VTE, the patient's risk of early (in-hospital or 30-day) death has been assessed by automated calculation of the original version of the Pulmonary Embolism Severity Index (PESI) after the acquisition of 11 different weighted

variables.[13] According to the results of the PESI score and in conjunction with hemodynamic instability, right ventricular dysfunction, elevated cardiac troponin levels and clinical parameters, patients were classified into high, intermediate-high, intermediate-low and low risk of early mortality.[10] PE was defined as massive in the presence of hemodynamic instability (cardiac arrest, obstructive shock or persistent hypotension), right ventricular dysfunction and elevated cardiac troponin levels.[10]

The inclusion of patients is illustrated in a consort diagram (Figure 1).

2.2 | Laboratory data

Plasma D-dimer concentrations (Roche Diagnostics) were measured on dedicated coagulation analyzers (CS-5100; Siemens Healthcare Diagnostics Products GmbH) using the Innovance D-dimer assay (Siemens Healthcare Diagnostics Products GmbH). D-dimer values <.5 mg/L were defined as normal and reported as fibrinogen equivalent units (FEUs) throughout the manuscript.

2.3 | Statistical analysis

Statistical analysis was performed using MEDCALC software (Version 19.7.0.). The normality of data distribution was evaluated using the Kolmogorov–Smirnov test. Continuous variables were presented as mean ± standard deviation (SD) or as median with 25th/75th percentiles (interquartile range, IQR). Categorical variables were presented as numbers with corresponding percentages. Comparisons between variables were conducted using chi-square statistic tests, one-way ANOVA, or two-tailed Student's *t*-test, where appropriate. Areas under the receiver operator characteristic (ROC) curve (AUCs) were calculated according to the methodology of DeLong. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of D-dimer were analysed at the recommended rule-out cut-off level of .5 mg/L. Furthermore, ROC-optimized cut-offs were calculated that balanced sensitivities and specificities for determining the best detection threshold for VTE.

Associations between D-dimer levels and outcomes were assessed with Cox regression analysis. All potential confounders were considered in the Cox regression model including variables that showed a significant association at *p*-values <.1 in univariate analysis. *p*-values <.05 were considered statistically significant.

3 | RESULTS

D-dimer concentrations were measured in a total of 526 cancer patients with a median age of 65 (range, 29–92;

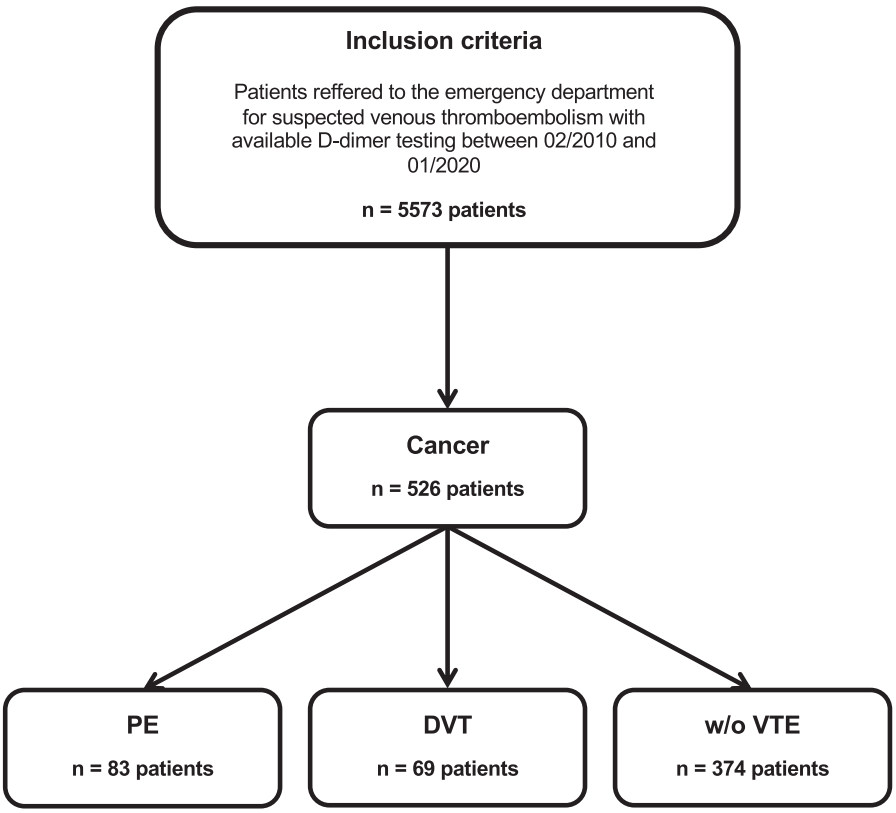

FIGURE 1 Recruitment of the study population. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

IQR, 55–75). Among these, 83 patients (16%) had PE, 69 (13%) DVT and 57 patients (11%) had both PE and DVT. Massive PE was observed in 19% of cases (16 of 83 patients). Bilateral DVT was registered in 29 of 69 patients (42%). Among the remainder, elevated D-dimer concentrations were observed in 206 patients who received a final diagnosis of pneumonia or other infection ($n = 57$), non-cardiac chest pain ($n = 41$), acute coronary syndrome ($n = 39$), lung disease ($n = 19$), acute or chronic heart failure ($n = 14$), peripheral arterial disease ($n = 12$), hypertensive crisis ($n = 11$), gastritis ($n = 6$), orthopaedic disease ($n = 4$) and aortic dissection ($n = 3$). The median Wells score was significantly lower in patients with DVT compared to those with PE (4, IQR 2–7 vs. 6, IQR 4–7; $p = .0031$). Dyspnoea (55%), swelling (24%) and pain (15%) of the lower limb, tachycardia (20%) and chest pain (14%) represented the most common symptoms among patients with cancer. Risk factors for thromboembolic diseases included smoking (20%), heart failure (15%), diabetes mellitus (8%), immobilization (7%) and a history of thromboembolic disease (7%).

The baseline characteristics of the study population are summarised in Table 1.

3.1 | Characteristics of D-dimers

D-dimer characteristics of the study population are displayed in Table 2 and Figure 2. Median plasma D-dimer concentrations in the entire study population were .7 mg/L (IQR .2–4.5). D-dimer values of patients with PE (8.0 mg/L, IQR 4.2–12.3) differed not significantly from patients with DVT (5.4 mg/L, IQR 3.3–9.4; $p = .0630$), but from those of patients without VTE (.4 mg/L, IQR .2–.9; $p < .0001$).

Regarding subtypes of cancer, patients with hematologic cancer revealed the highest D-dimer concentrations (3.7 mg/L, IQR .5–7.7), while patients with cancer of unknown primary origin had the lowest D-dimer levels (2.0 mg/L, IQR .8–3.7, $p = .2246$). Basic laboratory parameters other than D-dimers are illustrated in Table S1.

3.2 | Diagnostic performance of D-dimers to detect venous thromboembolism among cancer patients

We found an overall AUC of .942 (95% CI, .92–.96; $p < .0001$) for the discrimination of patients with VTE from controls, with an AUC of .950 (95% CI, .93–.97; $p < .0001$) for patients with PE, and an AUC of .932 (95% CI, .90–.95; $p < .0001$) for those with DVT, respectively (Figure 3).

Using *C*-statistics for the determination of optimal cut-offs to discriminate VTE, D-dimer concentrations of 9.9 mg/L showed the highest PPV of 96% (95% CI, 85–99) at a sensitivity and specificity of 30% and 100% (Figure S1). At the age-independent rule-out cut-off level of .5 mg/L, D-dimer showed a sensitivity of 100% for the detection of VTE but a specificity of 65%. To achieve acceptable specificities >95% for detecting VTE, the cut-off value had to be set to at least 4.9 mg/L, yielding a sensitivity of 64%. The performance of D-dimer testing to discriminate VTE at different cut-offs is displayed in Table 3.

3.3 | Prognostic role

A total of 37 cancer patients (7%) required intensive care treatment after admission to the emergency department. During a median follow-up of 30 months (IQR 22–70), a total of 88 deaths (17%) occurred, with 30 (36%) and 11 (16%) events in patients with PE and DVT, respectively. Increased D-dimer concentrations were positively correlated with mortality in both cancer patients with VTE ($p < .0001$) and without VTE ($p = .0008$) (Table 4). Moreover, a positive association of elevated D-dimer concentrations with the reoccurrence of VTE was observed ($p = .0299$).

4 | DISCUSSION

Due to its high NPV, D-dimer testing is currently recommended for ruling out VTE in outpatients with low or intermediate clinical pre-test probability.[10,14] In this context, the combination of clinical pre-test probability and D-dimer testing is regarded to be a highly effective and safe strategy to avoid unnecessary diagnostic workup.[15] However, the determination of D-dimers is still discouraged by international guidelines in patients with cancer because D-dimers may frequently be elevated without the presence of a thrombus.[9] In clinical routine, although discouraged, D-dimers are sometimes ordered at the physician's discretion. At present, there is no conclusive guidance for the interpretation and subsequent diagnostic management of cancer patients with elevated D-dimers, leading mostly to decisions based on empirical experiences and the patient's clinical context. Until recently, D-dimers were exclusively used for rule-out of VTE due to sensitivities and NPVs exceeding 95%.[10,16] During the COVID-19 pandemic, an increasing body of evidence accumulated that moderate elevations of D-dimers starting at a 3-times upper limit of normal (ULN) suggest the presence of VTE complicating SARS-CoV-2 (severe acute respiratory syndrome coronavirus

TABLE 1 Characteristics of the study population

Variables—*n* (%) or median (IQR)	Overall (*n* = 526; 100%)	PE (*n* = 83; 16%)	DVT (*n* = 69; 13%)	w/o VTE (*n* = 374; 71%)	*p*-value
Demographics					
Age, years	65 (55–75)	65 (58–76)	63 (51–74)	65 (55–75)	.1938
Male sex	279 (53%)	52 (63%)	30 (44%)	197 (53%)	
Female sex	247 (47%)	31 (37%)	39 (56%)	177 (47%)	
Clinical presentation					
First event	136 (26%)	77 (93%)	59 (86%)	—	
Pain at presentation	125 (24%)	65 (78%)	60 (87%)	—	
Atrial fibrillation	32 (6%)	4 (5%)	7 (10%)	21 (6%)	
Clinical prediction rule					
Wells score (original version)	2 (2–4)	6 (4–7)	4 (2–7)	2 (1–3)	<.0001
Types of cancer					
Gastrointestinal					
Gastric	18 (3%)	5 (6%)	1 (1%)	12 (3%)	
Colorectal	37 (7%)	9 (11%)	5 (7%)	23 (6%)	
Oesophageal	4 (1%)	1 (1%)	—	3 (1%)	
Liver	33 (6%)	6 (7%)	6 (9%)	21 (6%)	
Pancreatic	7 (1%)	2 (2%)	1 (1%)	4 (1%)	
Urological					
Prostate	51 (10%)	4 (5%)	6 (9%)	41 (11%)	
Bladder	12 (2%)	1 (1%)	—	11 (3%)	
Kidney	20 (4%)	3 (4%)	1 (1%)	16 (4%)	
Penile	1 (1%)	—	—	1 (1%)	
Gynaecological					
Ovarian	16 (3%)	3 (4%)	1 (1%)	12 (3%)	
Uterus	38 (7%)	6 (7%)	3 (4%)	29 (8%)	
Mamma	40 (8%)	4 (5%)	2 (3%)	34 (9%)	
Vagina	2 (1%)	—	—	2 (1%)	
Haematological					
Hodgkin lymphoma	14 (3%)	4 (5%)	2 (3%)	8 (2%)	
Non-Hodgkin lymphoma	6 (1%)	1 (1%)	—	5 (1%)	
Acute lymphocytic leukaemia	3 (1%)	—	2 (3%)	1 (1%)	
Chronic lymphocytic leukaemia	14 (3%)	5 (6%)	6 (9%)	3 (1%)	
Acute myeloid leukaemia	2 (1%)	1 (1%)	—	1 (1%)	
Chronic myeloid leukaemia	10 (2%)	3 (4%)	3 (4%)	4 (1%)	
Dermatological					
Melanoma	17 (3%)	2 (2%)	4 (6%)	11 (3%)	
Non-melanoma	25 (5%)	1 (1%)	7 (10%)	17 (5%)	
Lung					
Non-small-cell lung carcinoma	47 (9%)	6 (7%)	4 (6%)	37 (10%)	
Small-cell lung carcinoma	9 (2%)	1 (1%)	2 (3%)	6 (2%)	
Central nervous system					
Pilocytic astrocytoma	14 (3%)	3 (4%)	2 (3%)	9 (2%)	
Medulloblastomas	6 (1%)	—	2 (3%)	4 (1%)	
Diffuse astrocytoma	5 (1%)	1 (1%)	1 (1%)	3 (1%)	

(Continues)

TABLE 1 (Continued)

Variables—*n* (%) or median (IQR)	Overall (*n* = 526; 100%)	PE (*n* = 83; 16%)	DVT (*n* = 69; 13%)	w/o VTE (*n* = 374; 71%)	*p*-value
Thyroid					
Papillary carcinoma	23 (4%)	4 (5%)	3 (4%)	16 (4%)	
Follicular carcinoma	11 (2%)	—	1 (1%)	10 (3%)	
Medullary thyroid carcinoma	4 (1%)	—	—	4 (1%)	
Head and neck					
Squamous-cell carcinoma	27 (5%)	4 (5%)	4 (6%)	19 (5%)	
Adenocarcinoma	4 (1%)	1 (1%)	—	3 (1%)	
Cancer of unknown primary					
CUP	6 (1%)	2 (2%)	—	4 (1%)	
TNM classification					
T stage					
T1	122 (23%)	6 (7%)	9 (13%)	107 (29%)	
T2	141 (27%)	8 (10%)	19 (28%)	114 (31%)	
T3	124 (24%)	23 (28%)	14 (20%)	87 (23%)	
T4	139 (26%)	46 (55%)	27 (39%)	66 (18%)	
N stage					
N0	97 (18%)	15 (18%)	11 (16%)	71 (19%)	
N1	239 (45%)	35 (42%)	21 (30%)	183 (49%)	
N2	190 (36%)	33 (40%)	37 (54%)	120 (32%)	
M stage					
M0	400 (76%)	38 (46%)	44 (64%)	318 (85%)	
M1	126 (24%)	45 (54%)	25 (36%)	56 (15%)	
Symptoms					
Dyspnoea	289 (55%)	66 (80%)	12 (17%)	211 (56%)	
Chest pain	72 (14%)	49 (59%)	4 (6%)	19 (5%)	
Haemoptysis	7 (1%)	7 (8%)	—	—	
Limb swelling	127 (24%)	42 (51%)	46 (67%)	39 (10%)	
Leg pain	81 (15%)	36 (43%)	42 (61%)	3 (1%)	
Tachycardia	105 (20%)	48 (58%)	24 (35%)	33 (9%)	
Syncope	13 (3%)	5 (6%)	2 (3%)	6 (2%)	
Risk factors					
Diabetes mellitus	40 (8%)	9 (11%)	5 (7%)	26 (7%)	
Smoking	105 (20%)	21 (25%)	20 (29%)	64 (17%)	
Immobilization >3 days	34 (7%)	10 (12%)	12 (17%)	12 (3%)	
Family history	27 (5%)	6 (7%)	11 (16%)	10 (3%)	
Pregnancy	10 (2%)	1 (1%)	2 (3%)	7 (2%)	
Stroke	23 (4%)	3 (4%)	5 (7%)	15 (4%)	
History of VTE	37 (7%)	11 (13%)	18 (26%)	8 (2%)	
Coagulopathy	38 (7%)	9 (11%)	13 (19%)	16 (4%)	
Heart failure	77 (15%)	18 (22%)	10 (15%)	49 (13%)	

Abbreviations: DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; VTE, venous thromboembolism.

type 2) associated pneumonia.[17,18] A recent publication on 1334 patients admitted with suspected VTE found that D-dimer elevations of more than 10-times ULN were associated with PPVs >70% and >85% for the presence of VTE in patients with and without co-existing cancer, respectively,[6] suggesting not only a slightly inferior but also valuable diagnostic performance of D-dimer testing in cancer patients.

TABLE 2 Illustration of D-dimer concentrations, type of care, and outcomes

Variables—*n* (%) or median (IQR)	Overall (*n* = 526; 100%)	PE (*n* = 83; 16%)	DVT (*n* = 69; 13%)	w/o VTE (*n* = 374; 71%)	*p*-value
D-dimer (mg/L)	.7 (.2–4.5)	8.0 (4.2–12.3)	5.4 (3.3–9.4)	.4 (.2–.9)	<.0001
D-dimer levels according to cancer subtypes (mg/L)					
Gastrointestinal	1.2 (.4–7.5) (*n* = 99)	8.0 (3.6–12.3) (*n* = 23)	7.9 (2.7–13.0) (*n* = 13)	.5 (.2–1.4) (*n* = 63)	<.0001
Urological	.5 (.2–1.3) (*n* = 84)	6.7 (3.1–17.4) (*n* = 8)	6.7 (3.8–12.5) (*n* = 7)	.3 (.2–.7) (*n* = 69)	<.0001
Gynaecological	.6 (.3–1.9) (*n* = 96)	8.0 (3.2–12.4) (*n* = 13)	7.2 (3.1–10.9) (*n* = 6)	.3 (.2–.6) (*n* = 77)	<.0001
Haematological	3.7 (.5–7.7) (*n* = 49)	7.8 (6.5–13.8) (*n* = 14)	3.7 (1.9–6.7) (*n* = 13)	.4 (.2–2.1) (*n* = 22)	<.0001
Dermatological	.4 (.2–4.4) (*n* = 42)	4.6 (4.6–8.3) (*n* = 3)	4.5 (1.6–7.8) (*n* = 11)	.3 (.2–.4) (*n* = 28)	<.0001
Lung-CA	.8 (.3–4.8) (*n* = 56)	7.7 (5.8–12.3) (*n* = 7)	4.1 (3.5–9.6) (*n* = 6)	.5 (.2–1.4) (*n* = 43)	<.0001
CNS	2.6 (.2–7.5) (*n* = 25)	7.5 (4.5–11.1) (*n* = 4)	7.8 (3.0–18.1) (*n* = 5)	.6 (.2–3.1) (*n* = 16)	.0025
Thyroid-CA	.7 (.2–4.6) (*n* = 38)	13.6 (9.4–17.9) (*n* = 4)	6.8 (5.4–8.1) (*n* = 4)	.3 (.2–1.1) (*n* = 30)	<.0001
ENT-CA	.5 (.2–5.0) (*n* = 31)	10.7 (6.6–24.8) (*n* = 5)	5.6 (2.7–21.8) (*n* = 4)	.3 (.2–.6) (*n* = 22)	<.0001
CUP	2.0 (.8–3.7) (*n* = 6)	2.2 (1.0–3.4) (*n* = 2)	—	2.0 (.5–4.2) (*n* = 4)	.9840
Type of care					
Inpatient	124 (24%)	61 (74%)	24 (35%)	39 (10%)	
Intensive care	37 (7%)	8 (10%)	2 (3%)	27 (7%)	
Recurrence after VTE					
Recurrence-free	131 (25%)	76 (92%)	55 (80%)	—	
Recurrence	21 (4%)	7 (8%)	14 (20%)	—	
In-hospital death					
Overall	31 (6%)	9 (11%)	6 (9%)	16 (4%)	
VTE related	8 (2%)	5 (6%)	3 (4%)	—	
Cancer related	12 (2%)	1 (1%)	2 (3%)	9 (2%)	
Cardiovascular related	3 (1%)	2 (2%)	—	1 (1%)	
Sepsis related	6 (1%)	—	1 (1%)	5 (1%)	
Other reasons	2 (1%)	1 (1%)	—	1 (1%)	
Mortality					
All-cause death	88 (17%)	30 (36%)	11 (16%)	47 (13%)	
Cancer related	42 (8%)	14 (17%)	7 (10%)	21 (6%)	
Cardiovascular related	22 (4%)	8 (10%)	2 (3%)	12 (3%)	
Respiratory related	9 (2%)	3 (4%)	1 (1%)	5 (1%)	
Sepsis related	12 (2%)	4 (5%)	1 (1%)	7 (2%)	
Other reasons	3 (1%)	1 (1%)	—	2 (1%)	

Abbreviations: CA, cancer; CNS, central nervous system; CUP, cancer of unknown primary origin; DVT, deep vein thrombosis; ENT, ear-nose-throat; IQR, interquartile range; PE, pulmonary embolism; VTE, venous thromboembolism.

This study delivers important information on the diagnostic and prognostic value of D-dimer testing in cancer patients. Of note, D-dimers were collected at the attending physician's discretion and not encouraged by hospital protocols. We report three important findings. First, D-dimers can be used in cancer patients for the accurate rule-out of VTE with a sensitivity of 100% (95% CI, 98–100) and an NPV of 100% (95% CI, 97–100), if they are below the general rule-out cut-off of .5 mg/L, or only slightly above (<.6 mg/L). In this context, the proportion of cancer patients in our study with D-dimers below .5 or below .6 mg/L qualifying for rule-out is considerable at 32% and 37%, respectively. Second, if D-dimers are highly elevated above 10-times ULN they are associated with a high PPV for the presence of DVT or PE and should not be ignored. We observed a positive correlation of D-dimer concentrations with PPV, peaking at the ROC-optimal cut-off value of 9.9 mg/L at a PPV and NPV of 96% (95% CI, 85–99) and 78% (95% CI, 76–80), respectively. Conversely, patients at the rule-out cut-off level of .5 mg/L showed PPVs of 54%. Regarding its ability to discriminate PE and DVT from various conditions

without the presence of a thrombus, D-dimer testing showed outstanding diagnostic performance with AUC levels ≥.932 (95% CI, .90–.95). Third, elevated D-dimers carry important prognostic information. A gradual increase in risk for all-cause death over 1 year suggests that VTE is also an indicator of more aggressive or more extensive cancer. Our data on the relationship between cancer type and D-dimer concentration support this hypothesis. Furthermore, elevated D-dimer concentrations were associated with the reoccurrence of VTE.

In summary, our findings provide evidence that D-dimer testing may be used irrespective of the presence or absence of cancer. Moreover, our results suggest that the practical use can be extended from an aid to rule-out to an aid for rule-in, provided D-dimers exceed 10-times ULN. This threshold allows a diagnosis with a specificity and PPV of at least 90%.

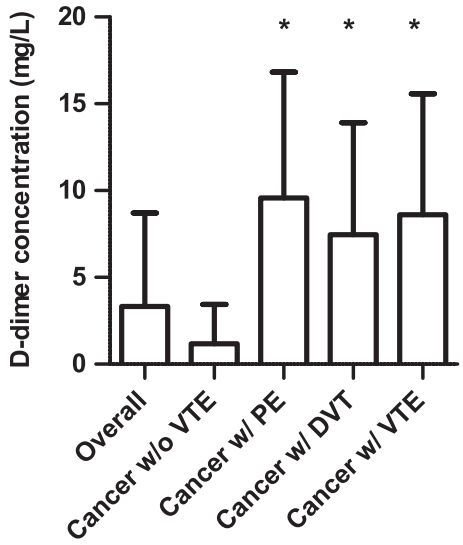

FIGURE 2 D-dimer concentrations of cancer patients at admission to the emergency department. *$p < .05$ versus cancer comparison group without VTE. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

4.1 | Previous findings on the usefulness of low D-dimers to rule out venous thromboembolism in cancer

In guidelines,[10,14] D-dimers are recommended only for rule-out in outpatients with low-to-intermediate pre-test probabilities. Commonly, testing of D-dimers is discouraged in patients with potentially confounding comorbidities such as, but not limited to, infections, inflammation, trauma, recent surgery or cancer.[9] To cope with the specificity issue, the most recent ESC Guidelines on PE introduced age-dependent cut-offs for patients aged 50 years or older and encouraged D-dimer testing during pregnancy, however indicating that elevated D-dimers may be anticipated beyond the first trimenon.[10] Conversely, the use of D-dimer in patients with cancer is still discouraged, partly due to a perceived lack of sensitivity and specificity. Recently, Koch et al.[6] reported on a large cohort of patients with suspected VTE where elevations of D-dimers above 10 times ULN were correlated with specificities and PPVs of approximately 80%, irrespective of the presence or absence of cancer.

Few studies have addressed the effectiveness of D-dimer testing for rule-out in cancer. While it is plausible that D-dimers below the common rule-out threshold can also accurately rule out VTE in cancer patients, there is only few data on the proportion of patients with cancer who qualify for rule-out. In a large multi-centre study of

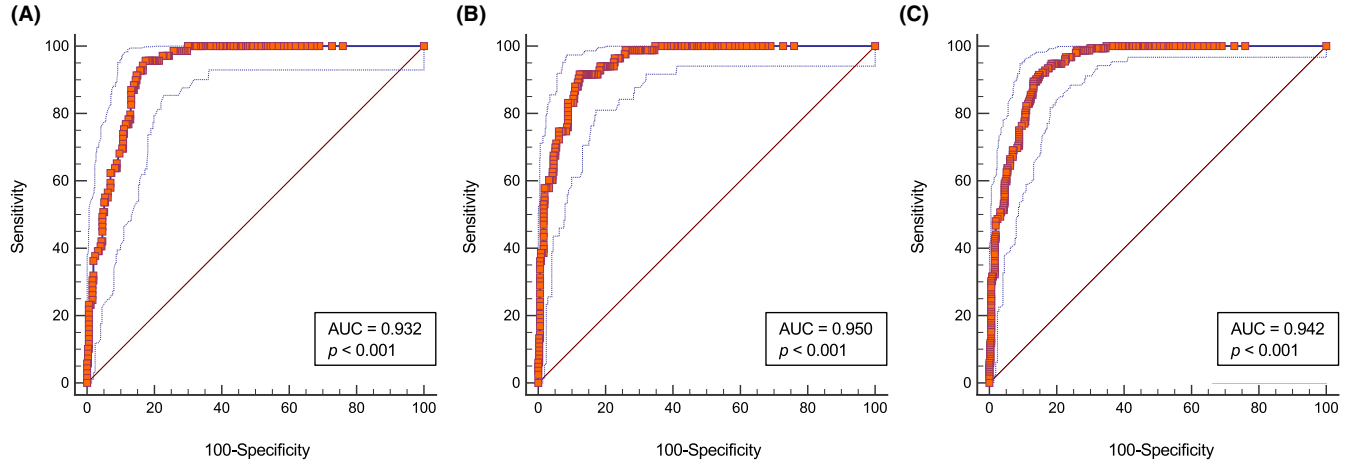

FIGURE 3 ROC curve analysis showing the diagnostic performance of D-dimer for detecting (A) DVT versus cancer patients w/o VTE, (B) PE versus cancer patients w/o VTE, and (C) VTE versus cancer patients w/o VTE. ROC curve data is depicted in red together with 95% confidence intervals in blue. DVT, deep vein thrombosis; PE, pulmonary embolism; ROC, receiver operating characteristic; VTE, venous thromboembolism

TABLE 3 Diagnostic performance of D-dimer testing at three different pre-specified cut-offs to discriminate PE and DVT

Disease entity	Cut-off (mg/L)	Sensitivity (%)	Specificity (%)	AUC	AUC (95% CI)	PLR	NLR	PPV (%)	NPV (%)	*p*-value (AUC)
Cancer patients ($n = 526$)										
Rule-out cut-off										
Overall VTE	.5	100	65	.942	.92–.96	2.9	0	53.9	100.0	<.0001
PE	.5	100	65	.950	.93–.97	2.9	0	39.0	100.0	<.0001
DVT	.5	100	70	.932	.90–.95	3.3	0	38.1	100.0	<.0001
95%-specificity cut-off										
Overall VTE	4.9	64	95	.942	.92–.96	11.9	.4	82.9	86.6	<.0001
PE	5.1	70	95	.950	.93–.97	13.8	.3	75.3	93.4	<.0001
DVT	4.7	55	95	.932	.90–.95	10.3	.5	65.5	91.9	<.0001
ROC-optimal cut-off										
Overall VTE	9.9	30	100	.942	.92–.96	56.6	.7	95.8	77.8	<.0001
PE	9.9	36	100	.950	.93–.97	67.6	.6	93.7	87.5	<.0001
DVT	9.6	23	99	.932	.90–.95	43.4	.8	88.9	87.5	<.0001

Abbreviations: AUC, area under the curve; CI, confidence interval; DVT, deep vein thrombosis; NLR, negative likelihood ratio; NPV, negative predictive value; PE, pulmonary embolism; PLR, positive likelihood ratio; PPV, positive predictive value; VTE, venous thromboembolism.

TABLE 4 Univariate and multivariable models for outcome prediction of D-dimers

	Endpoint 'death'		
	Exp(*b*)	95% CI of exp(*b*)	Overall model, *p*-value
(a) Model: Cancer with VTE			
Unadjusted model 1	1.1667	1.1279–1.2068	<.0001
Adjusted model 2	1.1482	1.1076–1.1902	<.0001
Adjusted model 3	1.1215	1.0764–1.1685	<.0001
(b) Model: Cancer w/o VTE			
Unadjusted model 1	1.1208	1.0652–1.1792	.0008

Note: Cox-regression models of cancer patients (a) with and (b) without VTE for death at follow-up. Model 1: an unadjusted basic model for D-dimer testing. Model 2: additionally adjusted by Wells score. Model 3: additionally adjusted by Wells score and family history. (a) Variables that did not reach univariate significance: hs-cTnT ($p = .5001$), age ($p = .1512$), sex ($p = .3054$), creatinine ($p = .5390$), C-reactive protein ($p = .2774$), leucocytes ($p = .2343$), NT-proBNP ($p = .1240$). Variables that reached univariate significance: Wells score ($p < .0001$), family history ($p < .0001$). (b) Variables that did not reach univariate significance: hs-cTnT ($p = .9248$), age ($p = .5923$), sex ($p = .1751$), creatinine ($p = .8016$), C-reactive protein ($p = .5657$), leucocytes ($p = .3475$), NT-proBNP ($p = .1227$), family history ($p = .1219$). Variables that reached univariate significance: N/A.

Abbreviations: *b*, regression coefficient; CI, confidence interval; Exp(*b*), ratio of hazard rates; hs-cTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VTE, venous thromboembolism.

474 cancer patients, the diagnostic strategy of D-dimer testing in combination with assessment of clinical pre-test probability has resulted in the rule-out of 49 patients (10%) at a very low failure rate of 2%.[19] However, only 12% had a normal D-dimer test below the rule-out cut-off <.5 mg/L, while studies in non-cancer populations allow the safe exclusion of approximately one-third of patients based on D-dimer testing and clinical pre-test probability.[20] In this study, the proportion was 32% suggesting that a relevant number of cancer patients could be tested in clinical routine. Additional studies are required to confirm our findings.

4.2 | Previous findings on the prognostic value of D-dimers

Traditionally, thrombus formation is thought to arise from vascular stasis, endothelial injury and hypercoagulability (Virchow's triad), frequently aggravating in cancer patients due to pro-coagulant effects of cancer therapies and tumour biology.[3] Concomitant VTE in cancer patients is known to affect survival adversely and represents a leading cause of death.[4,21] In our analysis of 526 patients with cancer, those with VTE were found to have a more aggressive and often advanced disease burden compared to patients without thromboembolic complications. Our data are consistent with other studies on the prognostic value of D-dimers in patients with cancer and VTE.[3,21–25] After adjustment for potential confounders, a diagnosis of thromboembolism at the time of or within 1 year of cancer diagnosis was found to predict death within that year for various cancer types that were evaluated.[21] Similarly, Sorensen et al. reported decreased survival for patients with simultaneously diagnosed thromboembolism and cancer compared to cancer patients without thromboembolism.[3] Further

studies are needed to explore other potential underlying mechanisms responsible for the extremely poor prognosis of cancer patients with VTE.

4.3 | Correlation of venous thromboembolism with cancer types and risk factors

Individuals with cancer commonly show multiple unique features to this population that should be considered in data analysis and interpretation. According to other studies,[26] we observed a significant impact of cancer subtypes on the likelihood of VTE occurrence. Whereas cancer patients with highly aggressive tumours (e.g. pancreas, ovarian or lymphoma) or advanced tumour stage were more frequently affected by VTE, patients with low-risk cancer (e.g. breast or prostate) or cancer at an early stage were less frequently involved. Thus, it appears that particularly biologically aggressive cancer subtypes, as evidenced by early metastatic spread and poor outcomes, are associated with a higher incidence of VTE.

Besides cancer-related factors that promote VTE, we observed many other conditions associated with an increased incidence of thromboembolic events, such as prolonged immobility, history of VTE and age. Additionally, the simultaneous presence and number of comorbidities have been shown to enhance the mortality rate.[27,28] In our study, cancer patients with VTE had a significantly higher cardiovascular risk profile than cancer patients without VTE (e.g. arterial hypertension, $p < .0001$). Consistently, in a retrospective analysis of 68,142 colorectal cancer patients, significant predictors of VTE were the presence of three or more comorbid conditions (hazard ratio, HR = 2.0; 95% CI, 1.7–2.3) and metastatic stage (HR = 3.2; 95% CI, 2.8–3.8).[27]

4.4 | Value of clinical prediction rules in cancer patients

Although being regarded as one of the best validated clinical prediction rules for VTE,[10] the Wells score has not yet been prospectively validated in individuals with cancer. This scoring system includes malignancy as a single variable but does not consider risk factors specific to cancer patients (e.g. chemotherapy). Considering more prevalent clinical signs and symptoms suggestive of VTE and the point score given for cancer, current clinical prediction rules tend to allocate cancer patients into higher risk categories.[29] Moreover, predictive values of variables might differ between cancer and non-cancer patients. Previous data indicated a lower performance of the Wells score to discriminate PE in cancer versus non-cancer patients.[30] Thus, the development and validation of cancer-specific clinical prediction rules are needed to improve the discriminative performance and clinical pre-test probability in patients with malignancies.

4.5 | Limitations

Our study has several limitations that need to be addressed. First, this study was conducted retrospectively at a single centre. Second, the measurement of D-dimers was performed at the sole discretion of the attending physician which may have caused selection bias. Third, our study suggests an association of D-dimers with all-cause mortality, raising the question of whether D-dimers only indicate a more aggressive cancer type or a higher prevalence of thromboembolic complications necessitating more intensive anticoagulation. Unfortunately, this study's retrospective design did not allow for addressing this question. Forthcoming studies are required to explore whether D-dimers could be used to guide the need and intensity of anticoagulation. Similar studies testing the benefits of prophylactic versus therapeutic anticoagulation in patients with SARS-CoV-2 used pre-specified D-dimer thresholds for study allocation. Fourth, more data from prospective trials are needed to assess D-dimer as a quantitative biomarker that can be used to rule in VTE in cancer or other patient populations. Prospective and multi-centre studies are also warranted to fully evaluate the economic burden related to test a high number of cancer patients for D-dimer at admission to the emergency department. Fifth, future studies with a clearer characterisation of cancer patients including those with active disease and in remission are necessary. Sixth, we did not collect information on anticoagulants before admission. Therefore, D-dimer levels may have been underestimated in the present investigation. Finally, cancer patients might have suffered from chronic forms of coagulation disorders that may typically result in chronic elevations of D-dimer concentrations in blood plasma. Therefore, a distortion of data cannot be completely excluded.

5 | CONCLUSION

Cancer-related thrombosis is the second leading cause of death in cancer patients and still represents a topic of valuable scientific impact. This work evaluated diagnostic cut-off concentrations of D-dimers, which might be helpful in daily clinical decision-making and risk stratification. Future studies are needed to investigate new diagnostic approaches and prediction rules to quickly identify cancer patients with a high risk of developing VTE.

AUTHOR CONTRIBUTIONS

All authors have contributed significantly to this work to merit co-authorship. Contribution to concept and design: V. Koch; S.S. Martin; T.J. Vogl; S.E. Hardt. Analysis and/or interpretation of data: V. Koch; J.-E. Scholtz; N.S. Ziegengeist; K. Torgashov; T. Geyer; L.D. Gruenewald; T. Gruber-Rouh; K. Eichler; C. Booz; T. D'Angelo; I. Yel. Critical writing: V. Koch. Revising the intellectual content: V.O. Puntmann; E. Nagel; S. Mahmoudi; D. Leistner; S. Bernatz; S.E. Hardt; L.S. Alizadeh. Final approval of the version to be published: T.J. Vogl; L.D. Gruenewald; E. Giannitsis.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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